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"Design, Synthesis, QSAR and Molecular Docking of some Polyhydroquinoline Derivatives"

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ABSTRACT:

In this study, the validation of the model was developed by using the MOO method (leave more out method) in order to obtain a very good model with a higher R^2 and a lower RMSE value. The statistical quality of the model was justified by statistical parameters such as the root mean square error (RMSE), correlation coefficient (R), square correlation coefficient (R^2), standard error of estimate (S), and (F- test value) or (the ratio between the variances of observed and calculated activities). Also, docking studies of these derivatives and their binding to the protein 4gdb were performed. Based upon molecular modeling and the validation QSAR equation, a group of polyhydroquinoline derivatives were synthesized by the four-component reaction of an aromatic aldehyde, 5, 5-dimethyl-1, 3-cyclohexanedione (dimedone), ethyl acetoacetate, and an appropriate amine for the synthesis. These procedures provide good yields.

KEYWORDS: Polyhydroquinolines (PHQs) derivatives**,** QSAR Study, Multi-component Reactions, and Molecular Docking.

1. Introduction

Polyhydroquinoline (PHQs) derivatives are of considerable interest due to their biological properties, which expand their applications as vasodilators, antitumor, bronchodilators, anti-atherosclerotic, gyro-protective, and heptoprotective agents (Nikpassand Mamaghani *et al*., 2009). Furthermore, these compounds exhibit diverse medicinal utility, such as neuroprotectant, platelet antiaggregatory activity, and chemsensitzer acting in tumor therapy (Safari Banitaba *et al.,* 2011).

Among the nitrogen heterocycles, polyhydroquinoline derivatives are a significant class of well-known calcium Ca^{+2} channel blockers and establish the skeletons of drug molecules utilized in the treatment of hypertension and cardiovascular diseases (Nishiya Kosaka *et al*., 2002).

Many types of models of QSARs are possible, with mathematical and statistical models being particularly common. Such models are often referred to as Quantitative Structure-Activity Relations (QSARs) or Quantitative Structure-Property Relations (QSPRs) (Tropsha Gramatica *et al*., 2003). Hansch was the first one to use QSARs to explain the biological activity of a series of structurally related molecules (Fujita Iwasa *et al.,* 1964; Hansch Lien *et al.,* 1968).

Docking of molecules is not an easy task. The difficulties are mainly associated with the choice of the crystallographic structure of a target protein. Some molecules may have a specific mechanism of chemical behavior associated with their unique binding properties. For instance, some molecules may have multiple binding modes, resulting in higher overall interaction energies in comparison with molecules with a single binding mode. Such a molecule could be attractive as a potential drug. Alkylating agents have been found to be potent anti-cancer agents (Gowramma Jubie *et al.*, 2009).

Multi-component reactions (MCRs) are convergent reactions in which three or more starting materials react to form a product, where basically all or most of the atoms contribute to the newly formed product. In an MCR, a product is assembled according to a cascade of elementary chemical reactions. Thus, there is a network of reaction equilibria that all finally flow

into an irreversible step, yielding the product. The challenge is to conduct an MCR in such a way that the network of pre-equilibrated reactions channels into the main product and does not yield side products. The result is clearly dependent on the reaction conditions: solvent, temperature, catalyst, concentration, the kind of starting materials and functional groups. Such considerations are of particular importance in the design and discovery of novel MCRs (Domoling, 2004).

In this study, a set of compounds of polyhydroquinoline derivatives and their calcium channel modulator activities were evaluated by quantitative structure-activity relationship analysis, and then all of them were subjected to molecular docking in order to find their binding affinities.

2. Experimental

2.1. QSAR Study

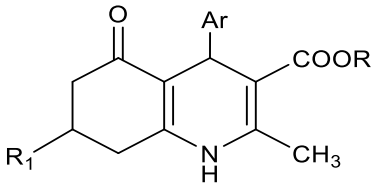
2.1.1. Data Set

In this QSAR studies, a total of substituted polyhydroquinoline derivatives as Calcium Channel Modulators, in rat ileum and rat thorasic aorta were utilized in this work (Gündüz Celebi *et al.*, 2009).

The set of substituted derivatives of polyhydroquinolines were divided into two sets, training set (10 compounds) and test set (5), by random selection.

The activity in terms of IC_{50} for training set and IC_{50} for test set compounds was expressed in microgram per milliliter were converted to the negative logarithmic concentration.

Table.1 : structures, IC_{50}, and PIC_{50} of the 7-substituted polyhydroquinoline Derivatives, the training set (Gündüz Celebi *et al.*, 2009).



Compound	R	R_1	Ar	IC_{50}	PIC_{50} (exp)	*PIC_{50} (pred)	Res
1/T	C_2H_5	CH_3	2,3-dichlorophenyl	57.83	4.24	PIC_{50} (Pred)	-0.0450
2	C_2H_5	CH_3	2,4-dichlorophenyl	40.00	4.40	4.2850	0.0677
3	CH_3	CH_3	2,5-dichlorophenyl	84.17	4.07	4.3323	-0.0452
4	C_2H_5	CH_3	2,5-dichlorophenyl	73.50	4.13	4.1152	-0.0175
5	CH_3	CH_3	2,6-dichlorophenyl	83.80	4.08	4.1475	0.0370

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6	CH_3	C_6H_5	2,3-dichlorophenyl	60.00	4.22	4.0430	-0.0218
7	CH_3	C_6H_5	2,5-dichlorophenyl	47.25	4.33	4.2418	0.0213
8	C_2H_5	C_6H_5	2,5-dichlorophenyl	52.13	4.28	4.3087	-0.0702
9	CH_3	C_6H_5	2,6-dichlorophenyl	46.00	4.34	4.3502	0.0713
10	C_2H_5	C_6H_5	2,6-dichlorophenyl	53.50	4.27	4.2687	0.0023
11/LO	C_2H_5	CH_3	2,6-dichlorophenyl	28.00	4.55	4.2677	0.0693
12/LO	C_2H_5	C_6H_5	2,3-dichlorophenyl	32.60	4.49	4.4807	-0.0836
13/T*	CH_3	CH_3	2,4-dichlorophenyl	24.00	4.62	4.5736	-0.0310
14/T*	CH_3	C_6H_5	2,4-dichlorophenyl	21.25	4.67	4.6510	-0.0722
15/T*	C_2H_5	C_6H_5	2,4-dichlorophenyl	13.53	4.87	4.7422	0.1175

T= Training set T*= Test set. LO = Leave one out. *PIC_{50} (pred), were predicted by equation (4)**2.1.2. Molecular Descriptors**

Molecular descriptor of the training set and test set compounds were chosen in order to deduce the good model, these descriptors involved total of Molecular descriptors for this group, 2D include: LogP(o/w), (octanol water partion coeffcent), TPSA (Topological Polar Surface Area), Weight (Molecular Weight), Density (Mass Density), and Mr (Molar refractivity). 3D descriptors include: AMI-IP, (Ionization Potential), dipole (dipole moment), PM3-IP (Ionization Potential), E (Potential Energy), PM3-E (Total Energy), and PM3-HF (Heat of Formation). Were calculated for training set and test set in table (2.2).

Table .2. Illustrates values of descriptors that calculated for training set, and test set compounds

o	AMI-IP	dipole	LogP(o/w)	PM3-IP	TPSA	weight	density	E	mr	PM3-E
	8.7418	1.6235	4.4440	8.7964	55.4000	394.298	0.8006	42.1155	10.3979	-100785.67
	8.7638	1.8271	4.4830	8.8232	55.4000	394.298	0.8006	35.3298	10.3941	-97336.796
	8.7099	0.9911	4.1420	8.7855	55.4000	380.271	0.8124	38.9999	9.9270	-100782.87
	8.6181	0.9416	4.4830	8.6816	55.4000	394.298	0.8006	37.5863	10.3941	-97332.632
	8.5100	0.6685	4.1030	8.6688	55.4000	380.271	0.8124	39.2247	9.9308	-97335.968
	8.6816	1.6207	4.1030	8.8050	55.4000	380.271	0.8124	44.2478	9.9308	-111686.91
	8.6377	1.3593	5.0750	8.7424	55.4000	442.342	0.7919	68.5937	11.9727	-115135.33
	8.6028	1.3537	5.4160	8.7475	55.4000	456.369	0.7827	58.0488	12.4400	-115135.33\
	8.5176	1.1912	5.0360	8.6706	55.4000	442.342	0.7919	68.4003	11.9764	-111684.50
	8.7986	0.9820	5.3770	8.9540	55.4000	456.369	0.7827	111.975	12.4437	-115105.28
D	8.4678	1.2315	4.4440	8.6431	55.4000	394.298	0.8006	37.4546	10.4440	-100781.13
D	8.5763	0.8004	5.3770	8.7215	55.4000	456.369	0.7827	62.7706	5.3770	-115134.04
*	8.7916	1.8308	4.1420	8.8357	55.4000	380.271	0.8124	37.4999	9.9270	-97337.046
*	8.7186	1.3957	5.0750	8.8294	55.4000	442.342	0.7919	57.6669	11.9727	-111689.25
*	8.5826	1.1838	4.4160	8.7418	55.4000	456.369	0.7827	56.2910	12.4400	-115136.17

T= Training set T*= Test set. LO = Leave one out.

2.1.3. Model Development

For each set of descriptors, the best multilinear regression equations were obtained by the stepwise selection methods of multiple linear regression (MLR) subroutine of spss software.

The QSAR model equation with High Square of the correlation coefficient (R^2) and low Root mean square error (RMSE) was QSAR equations:

PIC_{50}= 3.13653+0.21581*dipole+0.00201*weight……. (1)

PIC_{50}= 3.29567+0.21574*dipole+0.06096*mr…… (2)

PIC50= 4.15167+0.24335*dipole+0.00275*PM3-HF…. (3)

PIC_{50}= 3.39051+0.20874*dipole+0.12501*LogP (o/w) …….. (4)

PIC_{50}= 8.41367+0.19855*dipole-5.5494*density.... …..…….... (5)

The effect of these derivatives on the activity of calcium entry blockers was previously described using nonlinear quantitative structure-activity relationship (QSAR) models. QSAR analysis with various types of molecular descriptors was used to determine the effects of the structural parameters of the investigated polyhydroquinoline derivatives on their calcium channel blocker activity. The octanol-water partition coefficient (logp(o/w)) and dipole moment have been used as descriptors for bioavailability or the hydrophilic effect.

Equation (4) was the best QSAR model equation, with a high square of the correlation coefficient (R2= (0.81198) and a low Root Mean Square Error (RMSE = (0.04610),

2.1.4. Validation model

The validation of the model was developed by using MOO method (leave More out method) in order to obtain very good model with higher R^2 and low RMSE value.

2.8.2. Designing of Polyhydroquinoline Derivatives

Polyhydroquinoline derivatives have been reported to possess some interesting biological properties. Their biological activities were predicted by using the obtained predictive QSAR model No. (11) R^2 = (0.81).

Designed compounds gave biological activity (PIC_{50}), ranging from 3.89 to 4.53 M less than standard drug Nicardepine (PIC_{50}= 4.08).

The drug ability of designed derivatives was also evaluated through Lipinski‘s parameters and all within acceptable ranges of parameters shown in table (3.2). **Table .3.** Designed of some polyhydroquinoline derivatives with their predicted PIC_{50}

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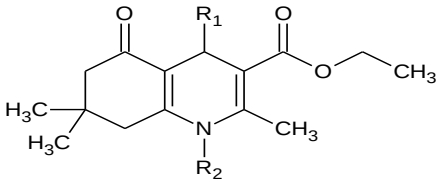
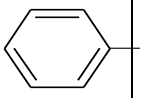
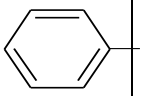
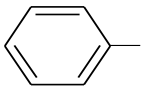
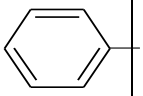
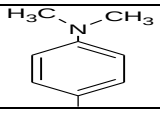
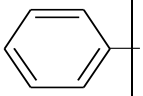
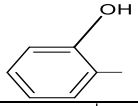
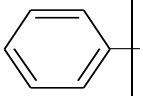
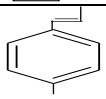
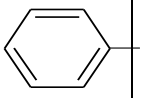
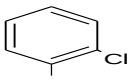
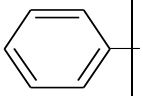
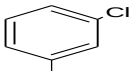
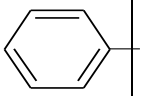
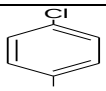
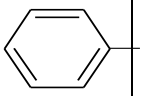
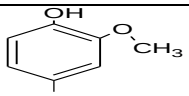
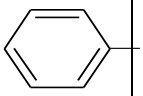
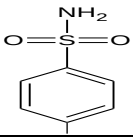
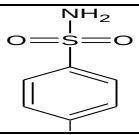
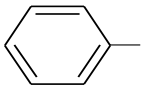
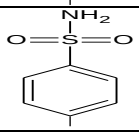
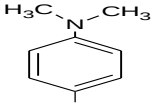
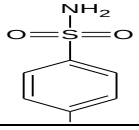
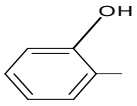
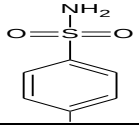
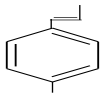
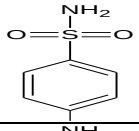
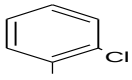
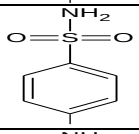
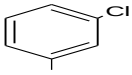
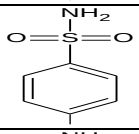
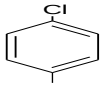
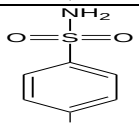
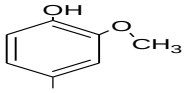
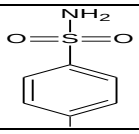


Com No.	R_1	R_2	AM1_IP	dipole	E	density	logP(o/w)	weight	LogP(o/w)
Q1	H		8.29026	1.2058	62.0470	0.697516	4.005	339.43	4.27
Q2	CH_3		8.37146	1.2004	65.6887	0.691621	4.375	353.46	4.34
Q3/1b			8.42195	1.2433	81.5941	0.690704	5.65	415.53	4.52
Q4/4b			7.97589	1.2087	97.6824	0.686151	5.565	458.60	4.40
Q5/2b			8.51627	1.3070	78.2524	0.707279	5.379	431.53	4.52
Q6			8.43818	1.1890	86.5120	0.685069	6.294	441.57	4.62
Q7			8.37494	0.7558	81.9823	0.728634	6.24	449.97	4.60
Q8			8.55014	0.9349	80.0269	0.728634	6.279	449.97	4.65
Q9			8.54258	1.3948	81.9230	0.728634	6.242	449.97	4.64
Q10			8.42585	0.5112	89.2226	0.715349	5.333	461.55	4.49
Q11	H		8.53858	0.9536	34.9903	0.775087	2.433	418.51	4.12
Q12	CH_3		8.62384	0.8556	38.9657	0.766392	2.803	432.54	4.19

										
Q13			8.69417	1.0713	52.2527	0.755212	4.078	494.61	4.39	
Q14			8.14064	1.0828	67.6231	0.745028	3.993	537.68	4.23	
Q15			8.75897	1.0267	51.8444	0.769626	3.807	510.61	4.36	
Q16/ 5b			8.68812	0.8323	60.3337	0.746037	4.722	520.65	4.47	
Q17			8.62517	0.8031	51.8396	0.788593	4.668	529.05	4.45	
Q18			8.80085	1.1551	54.5289	0.788593	4.707	529.05	4.50	
Q19			8.80326	1.1595	51.7898	0.788593	4.67	529.05	4.59	
Q20/ 3b			8.58614	0.6367	59.8400	0.773949	3.761	540.63	4.31	

*predicted (PIC_{50}) were calculated from QSAR model equation, No. (11).

*Q3 ,Q4, Q5,Q16,Q20 were selected for synthesis.

Table .4. Docking Studies 7- substituted polyhydroquinoline Derivatives.

العدد أربعون
تاريخ الإصدار: 2 – شباط – 2022 م
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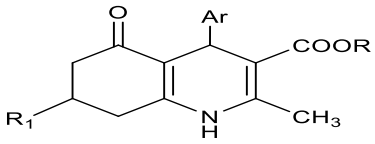
ISSN: 2663-5798



Entry	R	R_1	Ar	S Kcal/mol	rmsd	Amino acid	Group of interaction	Type of interaction	Length In (Å)
1	C_2H_5	CH_3	2,3-dichlorophenyl	262.26	1.10	AspA309 HisA194	N-H phenyl	H-bond π- bond -	2.10
2	C_2H_5	CH_3	2,4-dichlorophenyl	189.45	1.31	TrpA85	C=O phenyl	H-bond π- bond	2.82 -
3	CH_3	CH_3	2,5-dichlorophenyl	186.62	0.78	HisA194 SerA313 HisA221 HisA255	C=O C=O Phenyl Phenyl	H-bond H-bond π- bond π- bond	2.62 2.41 - -
4	C_2H_5	CH_3	2,5-dichlorophenyl	186.62	0.78	HisA194 SerA313 HisA221 HisA255	C=O C=O Phenyl Phenyl	H-bond H-bond π- bond π- bond	2.62 2.41 - -
5	CH_3	CH_3	2,6-dichlorophenyl	235.96	0.84	GluA101	N-H	H-bond	1.78
6	CH_3	C_6H_5	2,3-dichlorophenyl	235.95	0.84	GluA101	N-H	H-bond	1.79
7	CH_3	C_6H_5	2,5-dichlorophenyl	305.01	0.70	HisA74	Phenyl	π- bond	-
8	C_2H_5	C_6H_5	2,5-dichlorophenyl	177.52	0.92	HisA194 HisA194	C=O Phenyl	H-bond π- bond	2.38 -
9	CH_3	C_6H_5	2,6-dichlorophenyl	309.42	0.89	HisA221 - GluA101	Phenyl Phenyl N-H	π- bond π- bond H-bond	- - 3.25

10	C_2H_5	C_6H_5	2,6-dichlorophenyl	320.20	1.03	GluA101 -	N-H Zn^{2+} -cation	H-bond π- cation	2.16 -
11	C_2H_5	CH_3	2,6-dichlorophenyl	202.21	1.15	GluA101 -	N-H Zn^{2+} -cation	H-bond π- cation	1.97 -
12	C_2H_5	C_6H_5	2,3-dichlorophenyl	285.24	0.97	GluA101 HisA221 -	N-H Phenyl-Zn^{2+} cation	H-bond π- cation	2.25 - -
13	CH_3	CH_3	2,4-dichlorophenyl	195.94	1.39	GluA101 -	N-H Phenyl-Zn^{2+} cation	H-bond π- cation	1.77
14	CH_3	C_6H_5	2,4-dichlorophenyl	222.97	1.11	GluA101 HisA221 AspA309	N-H Phenyl Phenyl-Zn^{2+} cation	H-bond Π- bond π- cation π-cation	2.70 - - -
15	C_2H_5	C_6H_5	2,4-dichlorophenyl	309.32	1.13	GluA101 HisA221 -	N-H Phenyl Phenyl-Zn^{2+} cation	H-bond π- bond π- cation	2.41 - -
Nicardepine (a reference drug)			390.0632	1.2269		Trp-A85 His-A194 Trp-A85 Zn502	phenyl phenyl C=O C=O	π- bond π- bond H-bond π-cation	- - 5.10 -

3. Calculation of Statistical parameters

The statistical quality of the model was justified by statistical parameters such as the root mean square error (RMSE), correlation coefficient (R), square correlation coefficient (R^2), standard error of estimate(S), and (F- test value) or (the ratio between the variances of observed and calculated the activities).

Calculation of statistical parameter was carried out by using statistical programme SPSS version IBM-24

R=0.9011 R^2 = 0.812 RMSE=0.05156

Q= 0.7917 Q^2 = 0.6267 s= 0.021 F= 34.511 p= 0.0001

3. Docking studies

The (training set and test set), compounds were subjected to molecular docking in order to study their binding energy scores in the protein of 4gdb, compared to their reference drug(Nicardepine) and the result were tabulated in table (4).

العدد أربعون
تاريخ الإصدار: 2 – شباط – 2022 م
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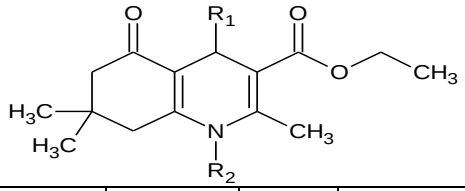
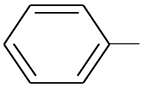
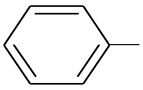
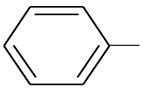
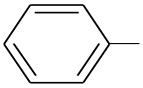
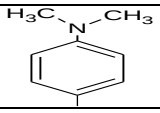
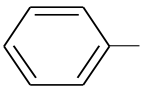
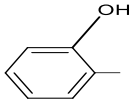
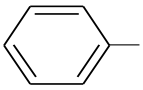
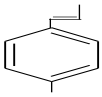
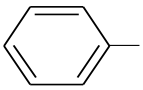
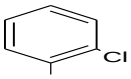
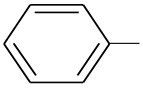
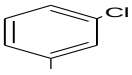
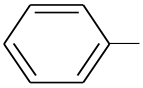
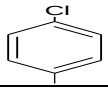
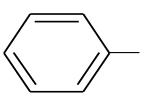
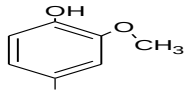
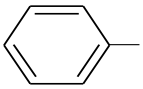
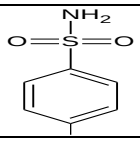
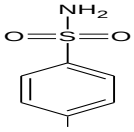
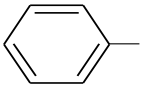
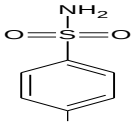
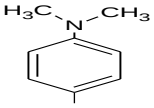
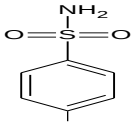
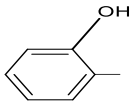
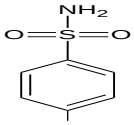
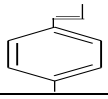
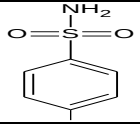
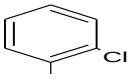
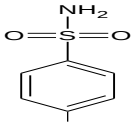
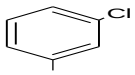
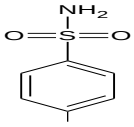
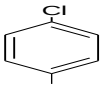
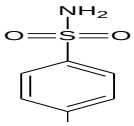
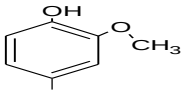
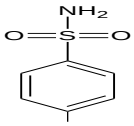
Table .5. Molecular docking of designed polyhydroquinoline derivatives



Entry	R1	R2	S	rmsd	Amino - acid	Group of interaction	Types of interaction	Length in (cÅ)
Q1	H		174.15	1.52	HisA194	Phenyl	π- bond	-
Q2	CH_3		209.74	1.16	HisA258 HisA74 AspA309 HisA72 HisA221	C=O C=O- Zn	H-bond π- cation	2.58 - - - -
Q3			434.75	1.15	HisA221 Zn502	C=O Phenyl	H-bond π- cation	2.55 -
Q4			475.64	1.12	HisA194 HisA194	C=O Phenyl	H-bond π- bond	2.26 -
Q5			425.60	1.45	TrpA98 Zn502	Phenyl Phenyl	π- bond π- cation	- -
Q6			233.18	1.78	GluA101 TrpA98 GlyA192 Zn502 HisA255	Phenyl Phenyl Phenyl Phenyl Phenyl	π- bond π- bond π- bond π- bond π- bond	- - - - -
Q7			488.89	1.09	HisA194 HisA194	C=O Phenyl	H-bond π- bond	2.19 -
Q8			385.03	1.23	HisA194 HisA194	C=O Phenyl	H-bond π- bond	2.30 -
Q9			424.72	1.01	HisA194 HisA255 HisA194	C=O C=O Phenyl	H-bond H-bond π- bond	2.35 2.28 -

					HisA221	Phenyl	π- bond	-
Q10			239.03	1.39	HisA255 GluA224 TrpA98 HisA255	CH_3O- O-H Phenyl Phenyl	H-bond H-bond π- bond π- bond	2.99 3.11 - -
Q11	H		208.62	1.21	ProA180	N-H	H-bond	3.81
Q12	CH_3		269.86	1.43	GluA101 TrpA98 HisA255 HisA194	N-H S=O C=O Phenyl	H-bond H-bond H-bond π- bond	1.98 2.79 2.49 -
Q13			413.95	1.53	HisA194 HisA194 HisA72 HisA74 AspA309 HisA221	C=O Phenyl C=O- Zn	H-bond π- bond π- cation π- cation π- cation π- cation	2.38 - - - - -
Q14			413.78	1.51	ProA180 TrpA98 HisA74 Zn502	N-H Phenyl Phenyl Phenyl	H-bond π- bond π- bond π- cation	6.66 - - -
Q15			501.50	1.37	GluA101 SerA313 HisA255 GluA224 TrpA98 Zn502	O-H S=O S=O N-H Phenyl Phenyl	H-bond H-bond H-bond H-bond π- bond π- cation	2.90 2.83 2.63 2.35 - -
Q16			264.83	1.30	HisA221 Zn502	Phenyl Phenyl	π- bond π- cation	- -
Q17			458.29	1.22	AspA309 GluA101 SerA313 SerA223 TrpA98	N-H N-H S=O S=O S=O	H-bond H-bond H-bond H-bond H-bond	1.77 2.14 2.37 2.25 2.78

ISSN: 2663-5798

					Zn502	Phenyl	π- cation	-
Q18			413.80	1.29	SerA223 AspA309 SerA313 SerA223 HisA221 Zn502	N-H N-H S=O S=O Phenyl Phenyl	H-bond H-bond H-bond H-bond π- bond π- cation	1.53 2.08 2.51 2.19 - -
Q19			555.74	1.28	GluA101 SerA223 SerA223 SerA313 AspA309 Zn502	N-H N-H N-H S=O S=O Phenyl	H-bond H-bond H-bond H-bond H-bond π- cation	1.64 2.39 2.46 2.26 2.61 -
Q20			577.12	1.37	TyrA197 HisA255 SerA223 HisA255 HisA221 HisA72 HisA74 HisA221 AspA309	C=O CH_3O- CH_3O- O-H O-H Zn502 Zn502 Zn502 Zn502	H-bond H-bond H-bond H-bond H-bond π- cation π- cation π- cation π- cation	2.37 3.12 3.22 2.27 2.46 - - - -

4. Results and Discussion

4.1. QSAR Study

Molecular descriptors can be calculated from the chemical formula (1D descriptors), the 2D structure (2D descriptors), and the 3D conformation (3D descriptors) using a large number of methods based on atom types, molecular fragments, and the three-dimensional structure, respectively (Bajot, 2010).

In this work QSAR study was carried out for 7-substituted derivatives of polyhydroquinoline. Data set was collected from literature (Gündüz Celebi *et al.*, 2009).Consist of 15 compounds table (1.1) and table (1.2) which is then divided into two sub set. Training set containing 10 compounds and test set of 5 compounds.

All descriptors were calculated by using MOE programme. For a statistically reliable model, the number of compounds and number of descriptors should bear a relation of at least 5:1. Thus, only two descriptors are required for 10 compounds in the

training set to develop statistically reliable QSAR model. Selection of a set of appropriate descriptors from a large number of them requires a method, which is able to distinguish between the parameters.

Person correlation matrix has been performed for all selected descriptors by using MOE software in order to select appropriate sub set descriptors. The analysis of these matrixes revealed appropriate 11 descriptors for the training set compounds.

QSAR models were developed during MLR analysis in training set with two descriptors and the best equation which showed high square correlation coefficient (R^2) and low root mean square error (RMSE) was considered as the best model with dipole and logP (o/w).

PIC_{50}= 3.39051+0.20874*dipole+0.12501*LogP (o/w)…… (4)

This developed QSAR model equation showed a relationship between in-vitro biological activities and correlated two descriptors dipole moment and logP (o/w). It is indicated that from the model equation that the molecular descriptors, namely logP (o/w) partition coefficient and dipole are positively correlated with PIC_{50}.

Database: e:/moe/bin-i4w9/ahmed(p2)

	1	2	3	4	5	6	7	8	9	10	11	12
1. PIC50	100	22	69	59	26	0	58	-62	30	58	-58	42
2. AM1_IP	22	100	46	2	90	0	-5	-10	28	-5	4	1
3. dipole	69	46	100	2	30	0	-2	-8	-21	-2	2	-18
4. logP(o/w)	59	2	2	100	24	0	99	-99	75	99	-99	87
5. PM3_IP	26	90	30	24	100	0	20	-27	60	20	-20	33
6. TPSA	0	0	0	0	0	100	0	0	0	0	0	0
7. Weight	58	-5	-2	99	20	0	100	-96	77	100	-100	92
8. density	-62	-10	-8	-99	-27	0	-96	100	-72	-96	96	-82
9. E	30	28	-21	75	60	0	77	-72	100	77	-77	92
10. mr	58	-5	-2	99	20	0	100	-96	77	100	-100	92
11. PM3_E	-58	4	2	-99	-20	0	-100	96	-77	-100	100	-91
12. PM3_HF	42	1	-18	87	33	0	92	-82	92	92	-91	100

Figure .1. Details of correlation matrix for molecular descriptors in training set compounds, polyhydroquinoline derivatives.

Internal validation by training Validation is a crucial aspect of any QSAR analysis, this step achieved by set compounds (cross validation) and external validation by test set compounds, also the (LMO), the leave more out method used to deduce very high $R^2$and low value of RMSE.

Internal validation by training set Validation is a crucial aspect of any QSAR analysis, this step achieved by set compounds (cross validation) and external validation by test set compounds.

The statistical fit of a QSAR can be assessed in many easily available statistical terms. The statistical quality of the resulting model is determined by R, $R^{2,}$ Q, Q^2, RMSE, S, F, and P value.

The QSAR model represents robustness, with good internal and external predictive capabilities and this model is acceptable because all the values of statistical measures are found to be in the acceptable ranges, the training set compounds:

R=0.9011 R^2 = 0.812 RMSE=0.05156

Q= 0.7917 Q^2 = 0.6267 s= 0.021 F= 34.511 p= 0.0001

One of the important characteristics of a QSAR model is its predictive power, (the ability of a model to predict accurately the biological activity of the compounds that were not is used for model development (external validation). Whereas, internal validation techniques described above can be used to establish model robustness, they do not directly assess model predictivity. In principle, external validation is the only way to determine the true predictive power of a QSAR model. This type of assessment requires the use of an external test set, compounds which not used for the model development.

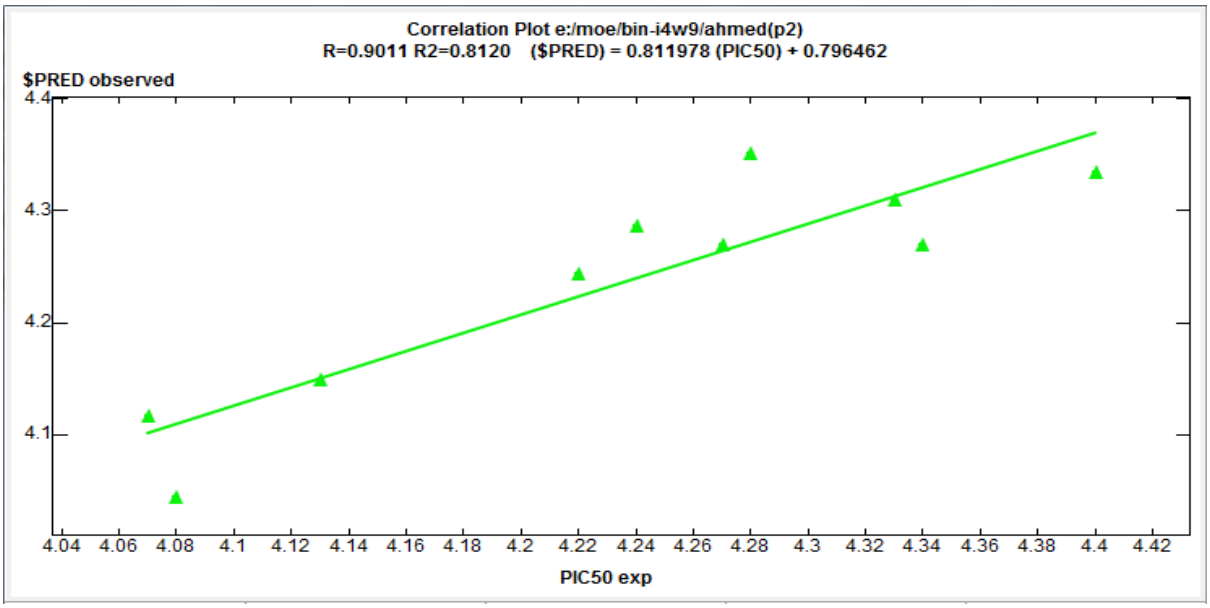


Figure .2. The plot of linear regression predicted PIC_{50} versus experimental values of the biological activity of training set compounds (validation).

العدد أربعون
تاريخ الإصدار: 2 – شباط – 2022 م
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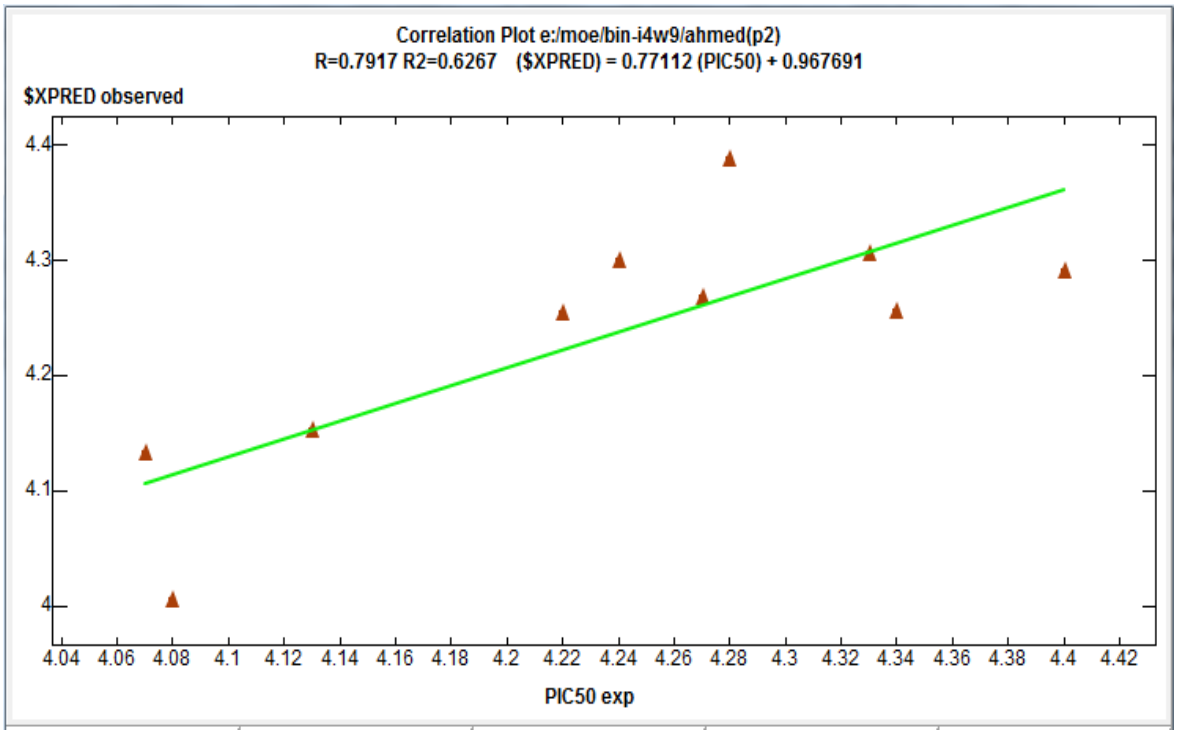
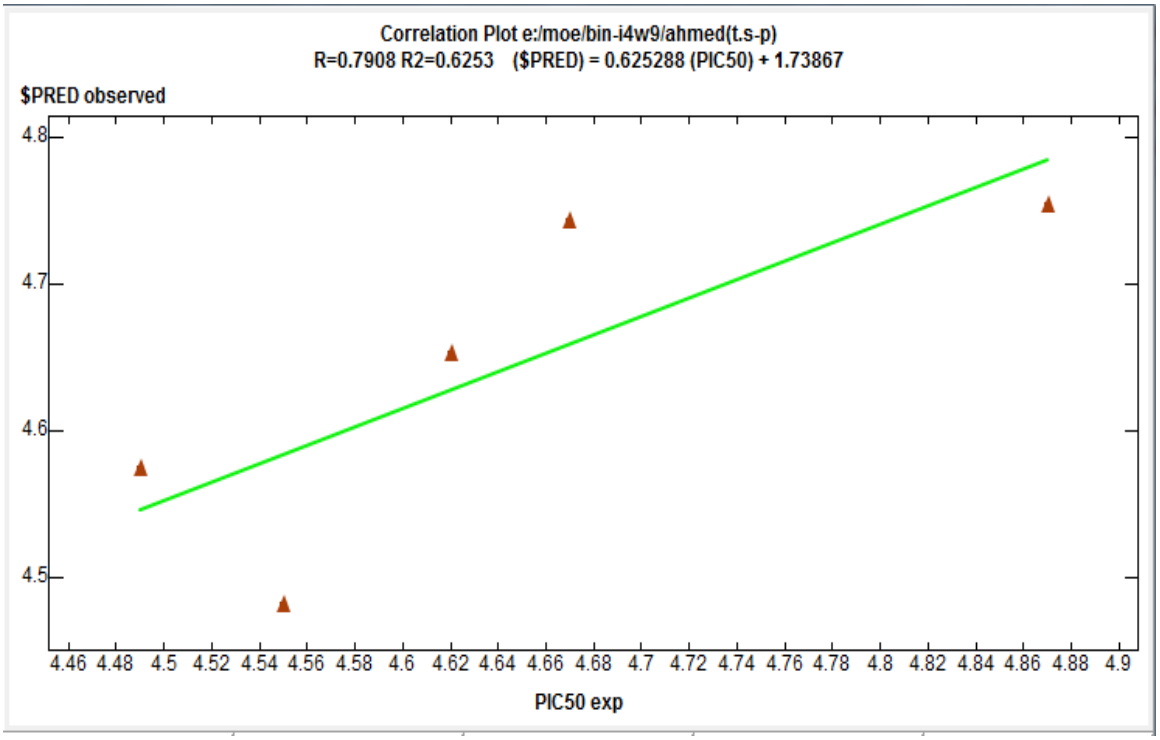


Figure .3. The plot of linear regression predicted PIC_{50} versus experimental values of the biological activity of training set compounds (cross-validation).



ISSN: 2663-5798

Figure .4. The plot of linear regression predicted PIC_{50} versus experimental values of the biological activity of test set compounds (validation).

5. Docking Study

Most of derivatives of 7-substituted polyhydroquinoline were tabulated in table (3.1). Thus, it was interesting to perform molecular docking to study the differences in docking patterns and amino acids interactions for the newly 7- substituted polyhydroquinoline derivatives. The protein 4gbd which was used to download the protein structure. All docking procedures were achieved by using MOE (Molecular Operating Environment) software, the docking protocol was verified by re-docking of the co-crystallized ligand (Nicardepine) in the vicinity of the active site of the protein with energy score(s) = 390.0549 kcal/mol, rmsd- refine = 1.2269.

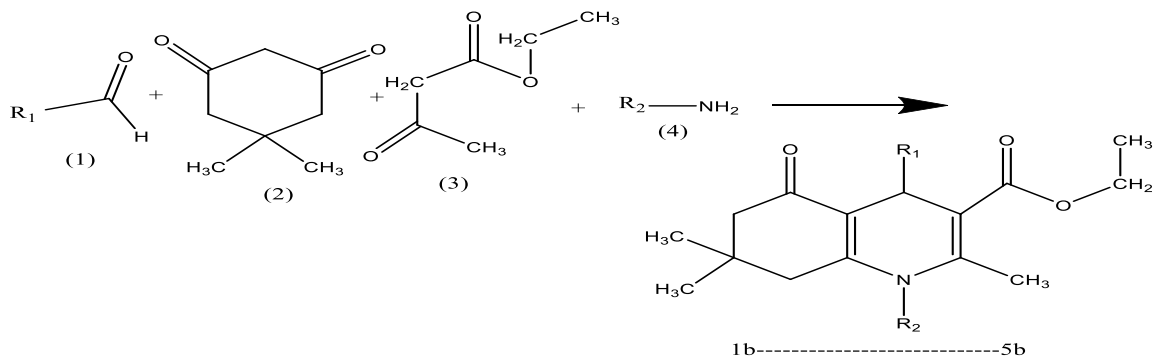
6. Organic Synthesis

6.1. General procedure for the preparation of Ethyl-2, 7, 7-trimethyl-5-oxo-1, 4, 5, 6, 7, 8-hexahydroquinoline-3-carboxylate derivatives 1b---3b

A mixture of aromatic aldehyde, (1mmol), 5, 5-dimethyl, 1, 3-cyclohexanedione (dimedone, 1 mmol), Ethyl acetoacetate, (1mmol), and appropriate amine, (1 mmol), in water 4ml were equipped in round-bottom flask fitted with reflux condenser, the reaction mixture was stirred vigorously under reflux for three hours at degree of temperature at 70^0C. The reaction mixture was then completed after this period of time, as monitored by using TLC, the workup procedure involved simple filtration and washing with cold ice water (10ml). The obtained pale yellow and yellow solid products of high purity was further achieved by recrystallization from aqueous ethanol.

6.2. General procedure for the preparation of Ethyl-2, 7, 7-trimethyl-5-oxo-1, 4, 5, 6, 7, 8-hexahydroquinoline-3-carboxylate derivatives 4b---5b

A mixture of Aldehyde, ethyl acetoacetate, dimedone, (any amine), and ethanol: water 1: 1 system 5ml was added to the mixture, then stirred and refluxed at 70^0C, for 6 hours. The reaction mixture was then completed after this period of time, as monitored by using TLC, the workup procedure involved simple filtration and washing with cold ice water (10ml). The obtained pale yellow solid product of high purity was further achieved by recrystallization from aqueous ethanol.



العدد أربعون
تاريخ الإصدار: 2 – شباط – 2022 م
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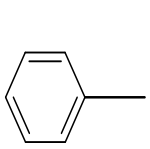
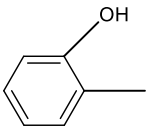
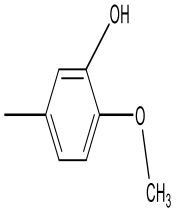
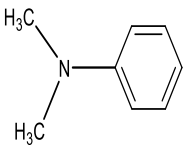
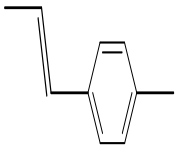
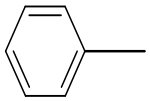
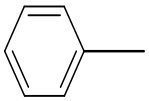
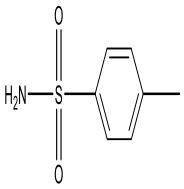
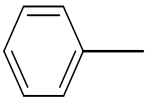
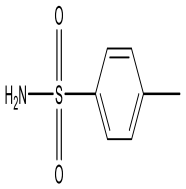
R_1					
R_2					

Scheme.1: Synthesis of polyhydroquinoline derivatives 1b-5b

All compounds exhibit good to excellent yields, except compound (2b)

6.3. Spectroscopic Analysis

Compound: Ethyl 2, 7, 7-trimethyl-5-oxo-1, 4-diphenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate(1b)

colour: yellow, yield%= 72.3, MP = 168- 170 ^{o}C, M.wt = 415, R_f = 0.89. IR (KBr): C-H Aliph, 2958 cm^{-1}, C=O, 1727; cm^{-1} C=C, 1591cm^{-1}.

^{1}H-NMR($CDCl_3$ (CH_3 ,6H,s), 0.191-1.176; (CH_2), 2.242; (CH_2), 1.010; (CH_3 ,3H,m), 1.852; (CH, 1H), 5.303; Phenyl ring, (5Hm).,7.113-7.190; Phenyl ring, (5Hm), 7.284-7592.

Ethyl 4-(2-hydroxyphenyl)-2,7,7-trimethyl-5-oxo-1-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate(2b)

colour: pale yellow, yield%= 53.6, MP = 161- 163 ^{o}C, M.wt = 431, R_f = 0.96. IR (KBr): C-H Aliph2955cm^{-1}; C=O, 1723 cm^{-1}; C=O, 1640 cm^{-1}; OH (bonded) , range 3200-3500 cm^{-1}. ^{1}H-NMR ($CDCl_3$ (CH_3 ,6H,s), 0.858-1.045; (CH_2), 2.007; (CH_2), 2.22; (CH, 1H), 2.48; Phenyl ring, (4Hq); 7.02-7.22; Phenyl ring, (5Hm), 7.23-7.43; OH(1H), 13.055.

Ethyl 4-(3-hydroxy-4-methoxyphenyl)-2,7,7-trimethyl-5-oxo-1-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate(3b)

colour: pale yellow, yield% = 84.3, MP = 198- 200 ^{o}C, M.wt = 540, R_f = 0.76. IR (KBr); N-H st.vib, 3485 cm^{-1} OH (bonded), range 3200-3500 cm^{-1}; C=O, 1731 cm^{-1}; C=C, 1590 cm^{-1}. ^{1}H-NMR ($CDCl_3$ (CH_3 ,6H, s), 1.028-1.274; (CH_2), 5.303; (CH_2), 2.328; (CH, 1H), 4.69; (CH_3 ,3H, m), 2.242, Phenyl ring, (3Ht), 7.078-7.190; Phenyl ring, (5Hm), 7.28-7.59; OH(1H), 11.933; (CH_3 ,3H, s), 3.87.

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Ethyl 4-(4-(dimethyl amino) phenyl) - 2, 7, 7-trimethyl-5-oxo-1-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate(4b)

colour: yellow, yield%= 85.8, MP= 180-182 ºC, M.wt = 458, R_f = 0.65. IR(KBr); C-H, 2954 cm^{-1}; ; C=O, 1716 cm^{-1} ; ^{1}H-NMR($CDCl_3$ (CH_3 ,6H,s), 0.907-1.025; (CH_2), 2.268; (CH_2), 2.307; (CH_3 ,3H,m), 2.24 ; (CH, 1H), 2.17.

(CH_3, 6H, s), 2.259; Phenyl ring, (4H, m), 7.123-7.189; Phenyl ring, (5H, m), 7.304-7.37.

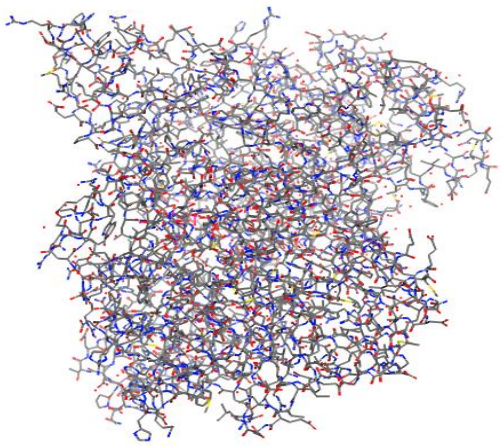
(E)-2, 7, 7-trimethyl-5-oxo-4-styryl-1-(4-sulfamoylphenyl)-1, 4, 5, 6, 7, 8-hexahydroquinoline-3-carboxylate(5b)

color: pale yellow, yield%= 88.7, MP = 188-191 ºC, M.wt = 520, R_f = 0.60. IR(KBr): N-H st.vib, 3421 cm^{-1} ; C-H, 2956 cm^{-1}; C=O, 1714 cm^{-1} C=O, 1630cm^{-1} ; ^{1}H-NMR($CDCl_3$ (CH_3 ,6H,s), 1.023-1.088; (CH_2), 1.170; (CH_2 1.183; (CH, 1H), 1.185; (CH_3, 3H, s), 1.280; (CH_2), 2.348; (CH_3, 3H, s), 2.577; (CH, 1H), 3.326; (CH, 1H), 2.43; (CH, 1H), 4.091; Phenyl ring, (5H,m), 7.116-7.212; Phenyl ring, (5H,m), 7.31-7.320; (NH_2, 2H), 2.404.

7. Conclusion

Validation of the model using a suitable statistical algorithm becomes essential to confirm the stability and predictivity of the model. In this study we used suitable molecular descriptors in order to get good model to predict the biological activities for these derivatives, also molecular docking studies shows good binding energies. Some derivatives were synthesized by using appropriate procedures. These general and efficient procedures offer several advantages including the usage of dual solvent system, wide scope of substrates, usage of very cheap and readily available Cetyl Trimethyl Ammonium Bromide (CTAB), a phase- transfer catalyst to the reaction mixtures as a catalyst, high yield and the facile separation of the products by simple filteration after washing with water. All of these points make this procedure as a very useful and practical alternative in the synthesis of these compounds.

Figure .5. 3D of 4gbd protein



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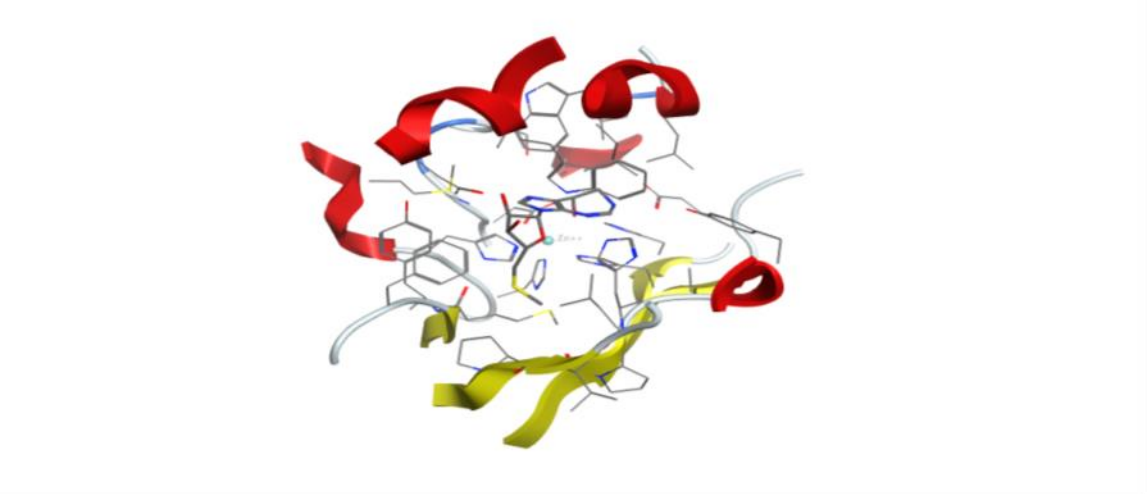

Figure .6. the pocket and ligand of 4gbd protein.

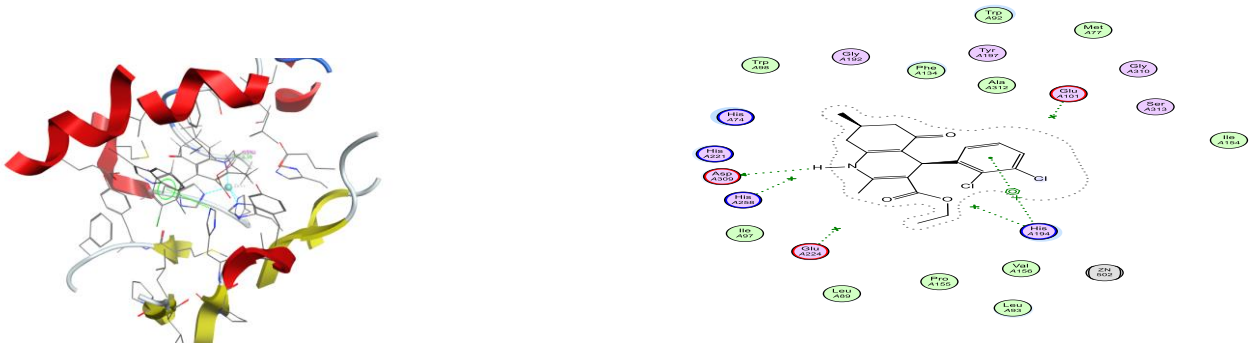

Figure 7. Showed 3D and 2D, interaction of ethyl 4-(2, 3-dichlorophenyl)-2, 7-dimethyl-5-oxo-1, 4, 5, 6, 7, 8-hexahydroquinoline-3-carboxylate (1) inside the active site of 4gdb protein.

العدد أربعون
تاريخ الإصدار: 2 – شباط – 2022 م
www.ajsp.net
ISSN: 2663-5798

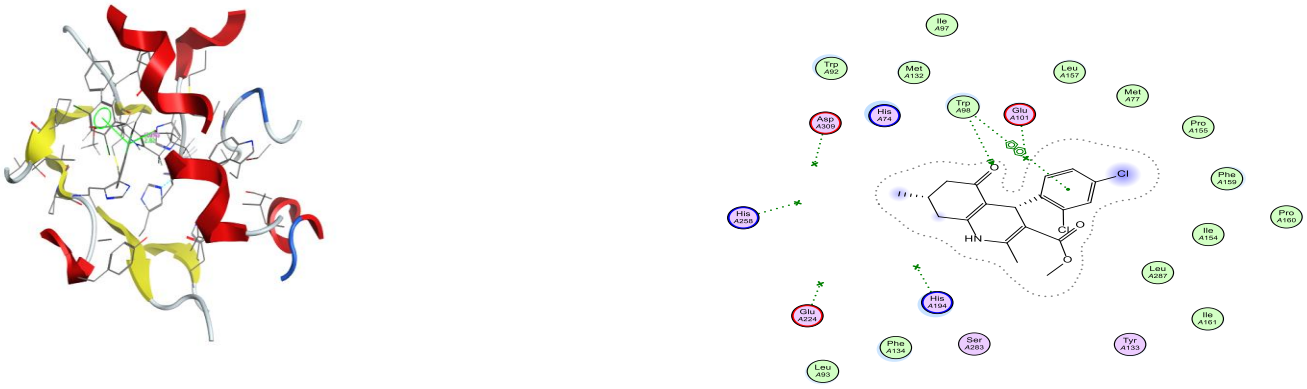

Figure 8. Showed 3D and 2D, interaction of methyl 4-(2,4-dichlorophenyl)-2,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (2) inside the active site of 4gdb protein.

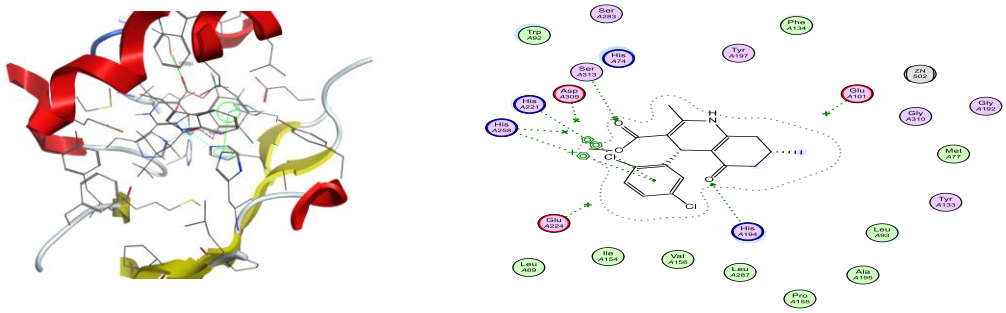

Figure 9. Showed 3D and 2D, interaction of methyl 4-(2,5-dichlorophenyl)-2,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate(3) inside the active site of 4gdb protein.

العدد أربعون
تاريخ الإصدار: 2 – شباط – 2022 م
www.ajsp.net
ISSN: 2663-5798

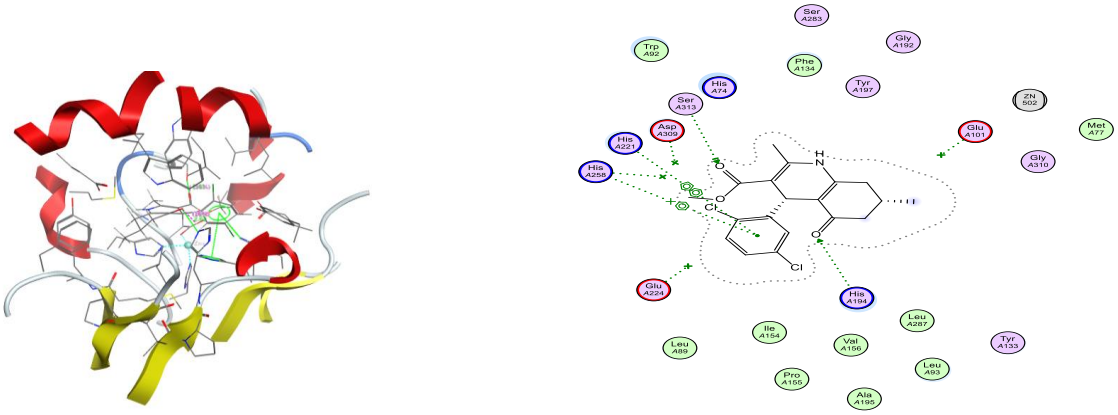

Figure 10. Showed 3D and 2D, interaction of. ethyl 4-(2,5-dichlorophenyl)-2,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate(4) inside the active site of 4gdb protein.

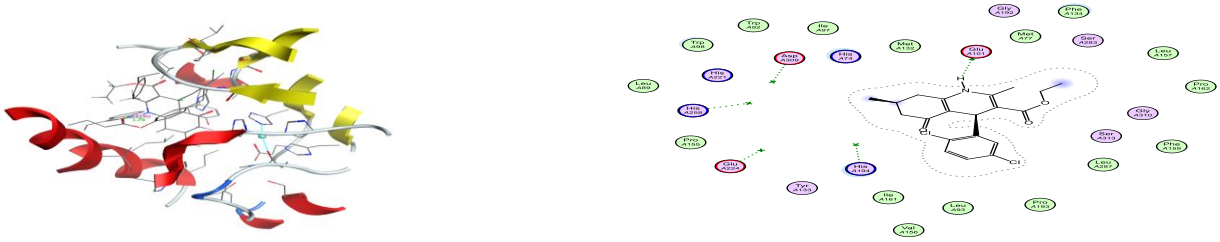

Figure 11. Showed 3D and 2D, interaction of. methyl 4-(2,5-dichlorophenyl)-2,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5) inside the active site of 4gdb protein.

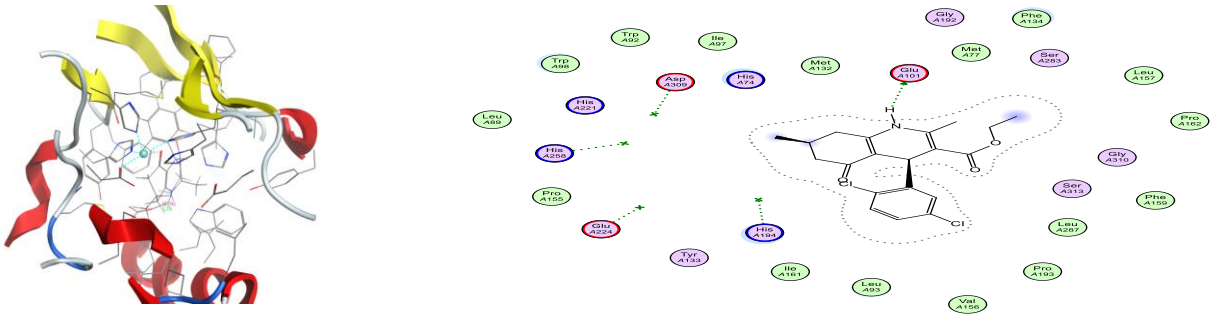

Figure 12. Showed 3D and 2D, interaction of ethyl 4-(2,5-dichlorophenyl)-2,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (6) inside the active site of 4gdb protein.

العدد أربعون
تاريخ الإصدار: 2 – شباط – 2022 م
www.ajsp.net
ISSN: 2663-5798

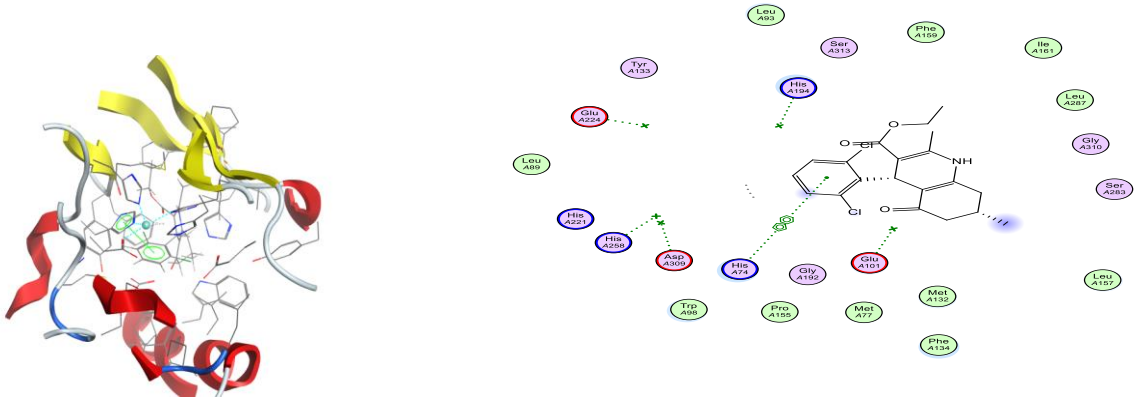

Figure 13. Showed 3D and 2D, interaction of ethyl 4-(2-chloro-6-methylphenyl)-2,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (7) inside the active site of 4gdb protein.

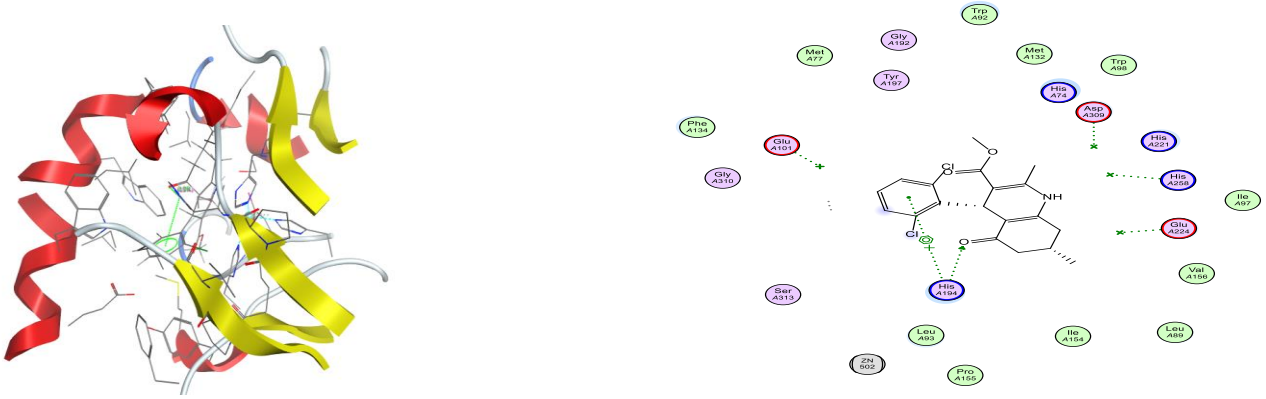

Figure 14. Showed 3D and 2D, interaction of. methyl 4-(2-chloro-6-methylphenyl)-2,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (8) inside the active site of 4gdb protein.

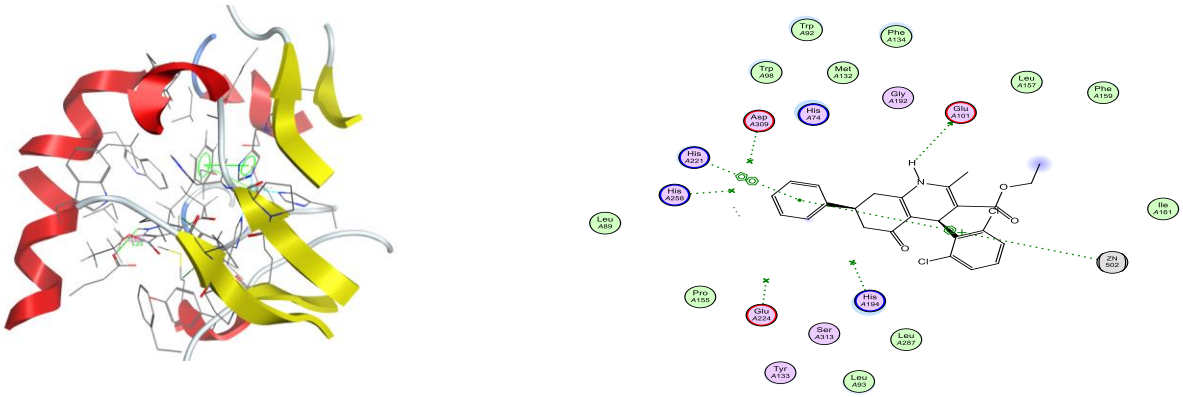

Figure 15. Showed 3D and 2D, interaction of ethyl4-(2,6-dichlorophenyl)-2-methyl-5-oxo-7-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (9) inside the active site of 4gdb protein.

العدد أربعون
تاريخ الإصدار: 2 – شباط – 2022 م
www.ajsp.net
ISSN: 2663-5798

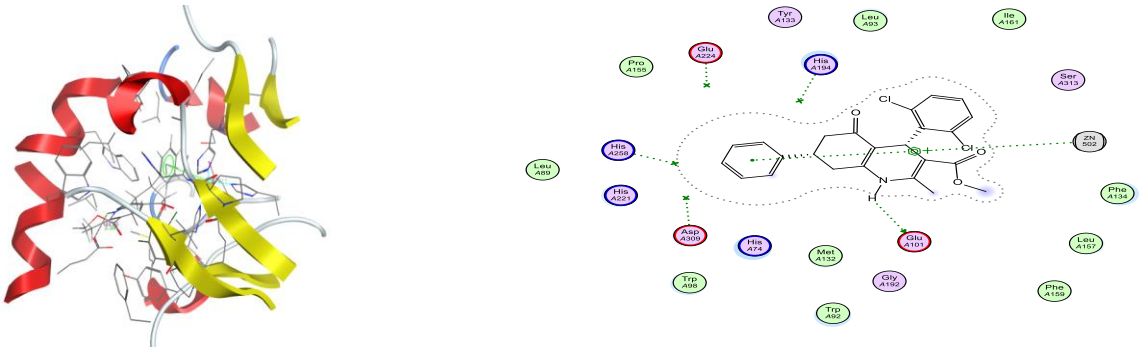

Figure 16. Showed 3D and 2D, interaction of methyl 4-(2,6-dichlorophenyl)-2-methyl-5-oxo-7-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (10) inside the active site of 4gdb protein.

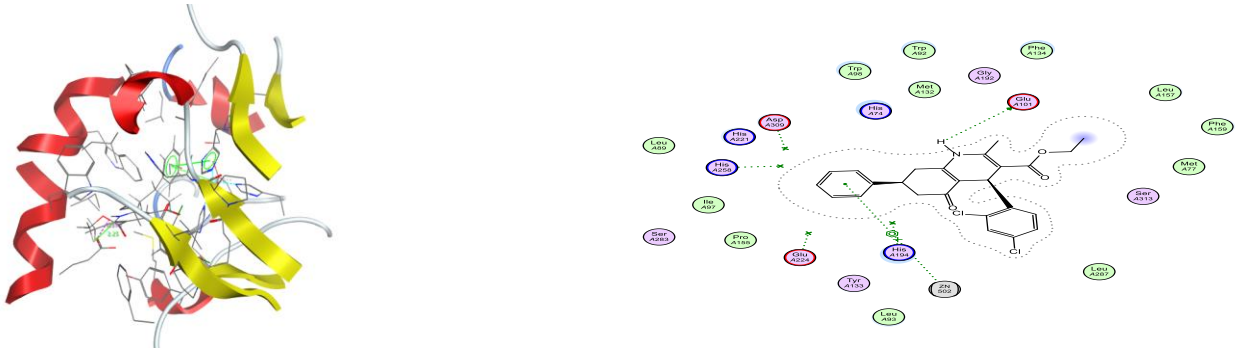

Figure 17. Showed 3D and 2D, interaction of ethyl 4-(2,4-dichlorophenyl)-2-methyl-5-oxo-7-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (11) inside the active site of 4gdb protein.

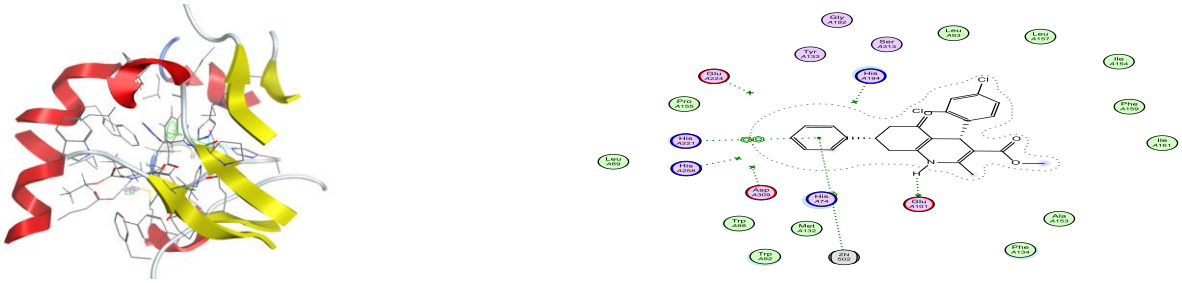

Figure 18. Showed 3D and 2D, interaction of methyl 4-(2,4-

dichlorophenyl)-2-methyl-5-oxo-7-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (12) inside the active site of 4gdb protein.

العدد أربعون
تاريخ الإصدار: 2 – شباط – 2022 م
www.ajsp.net
ISSN: 2663-5798

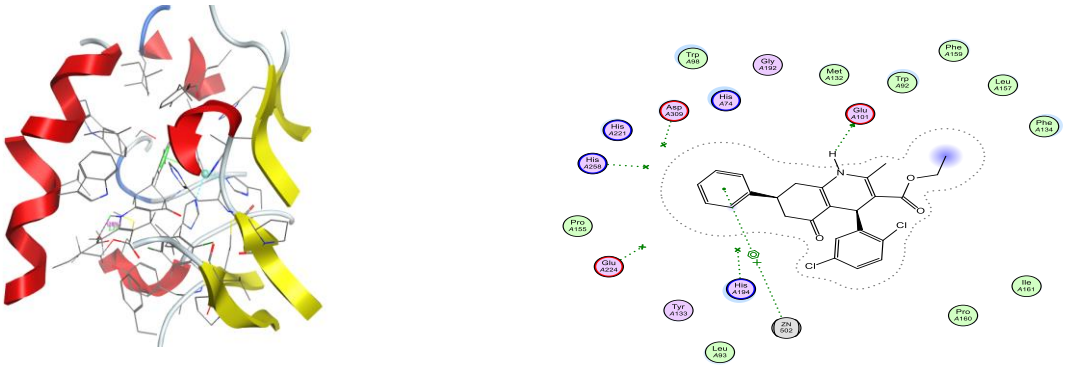

Figure 19. Showed 3D and 2D, interaction of ethyl 4-(2,5-dichlorophenyl)-2-methyl-5-oxo-7-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (13) inside the active site of 4gdb protein.

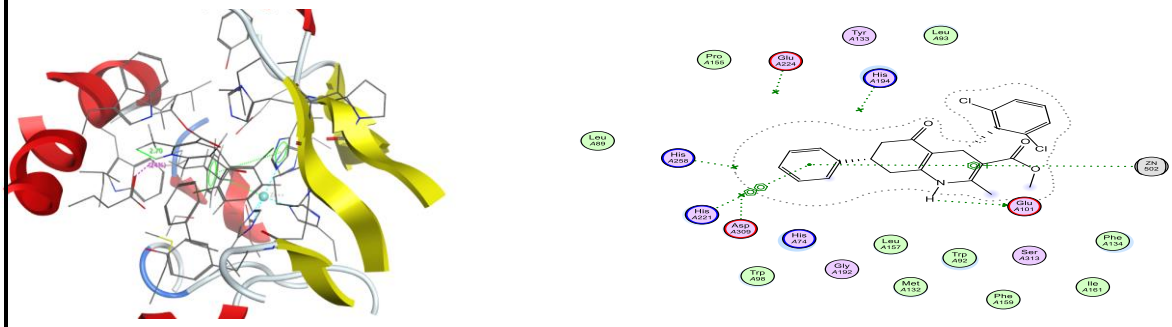

Figure 20. Showed 3D and 2D, interaction of methyl 4-(2,6-dichlorophenyl)-2-methyl-5-oxo-7-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (14) inside the active site of 4gdb protein.

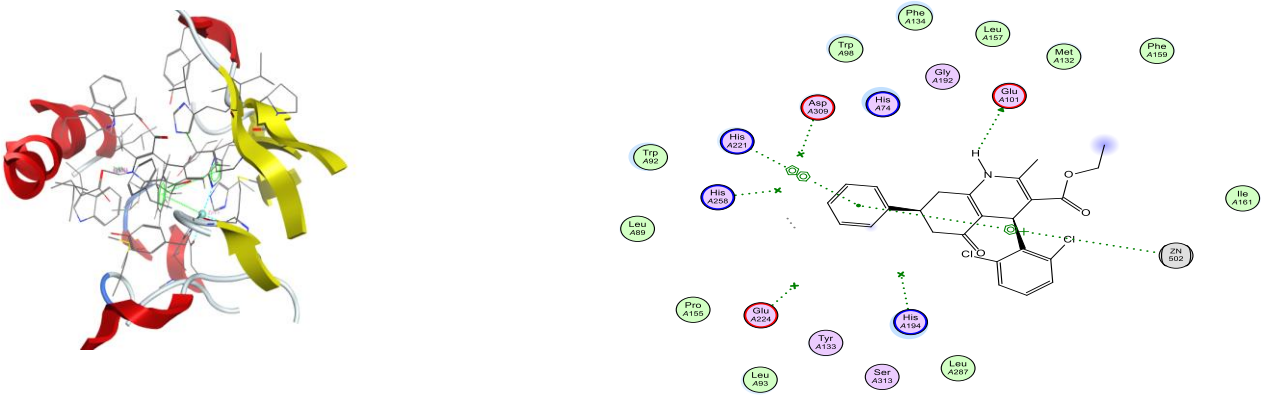

Figure 21. Showed 3D and 2D, interaction of ethyl 4-(2,6-dichlorophenyl)-2-methyl-5-oxo-7-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (15) inside the active site of 4gdb protein.

العدد أربعون
تاريخ الإصدار: 2 – شباط – 2022 م
www.ajsp.net
ISSN: 2663-5798

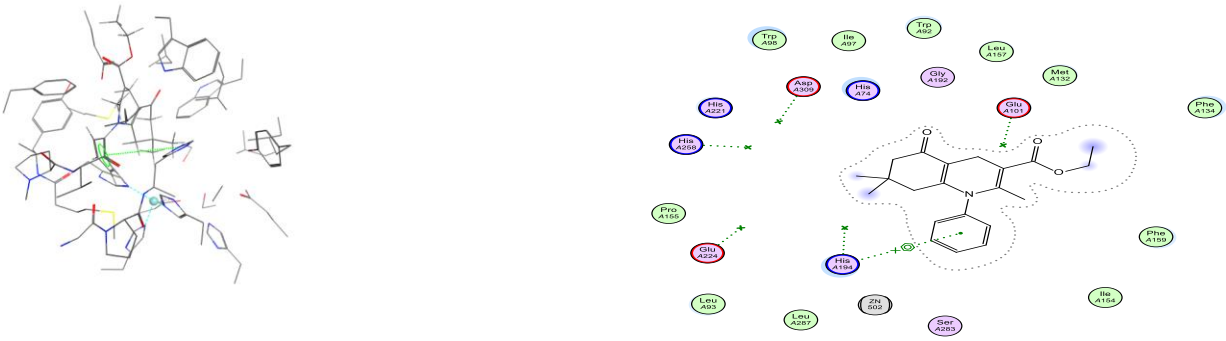

Figure22. Showed 3D and 2D, interaction of Q1. Ethyl 2,7,7-trimethyl-5-oxo-1-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate inside the active site of 4gdb protein.

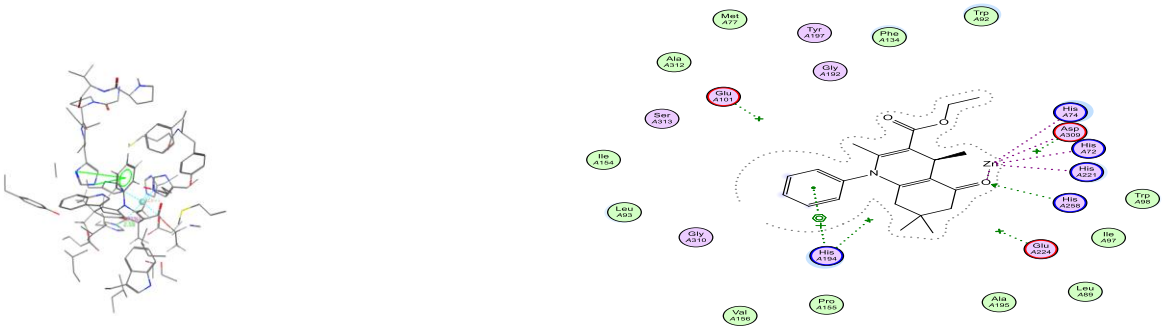

Figure23. Showed 3D and 2D, interaction of Q2. Ethyl 2,4,7,7-tetramethyl-5-oxo-1-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate inside the active site of 4gdb protein.

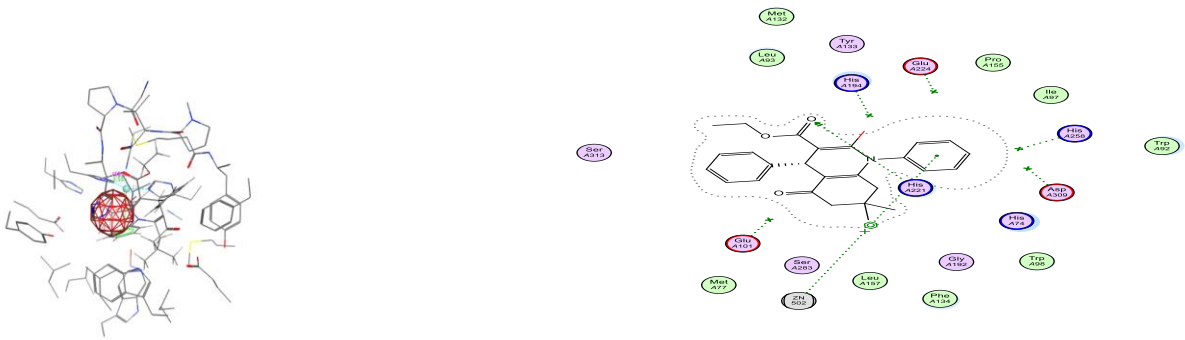

Figure24. Showed 3D and 2D, interaction of Q3. Ethyl 2,7,7-trimethyl-5-oxo-1,4-diphenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate inside the active site of 4gdb protein.

العدد أربعون
تاريخ الإصدار: 2 – شباط – 2022 م
www.ajsp.net
ISSN: 2663-5798

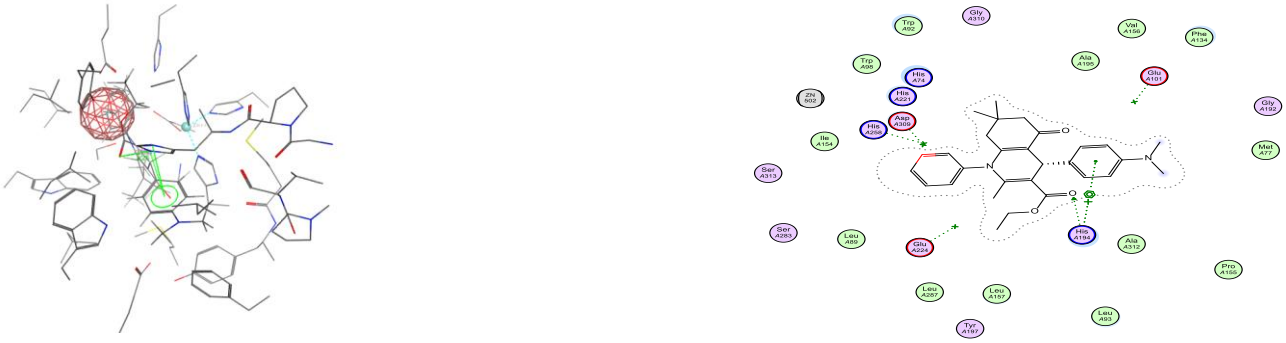

Figure25. Showed 3D and 2D, interaction of Q4. Ethyl 4-(4-(dimethylamino)phenyl)-2,7,7-trimethyl-5-oxo-1-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate inside the active site of 4gdb protein.

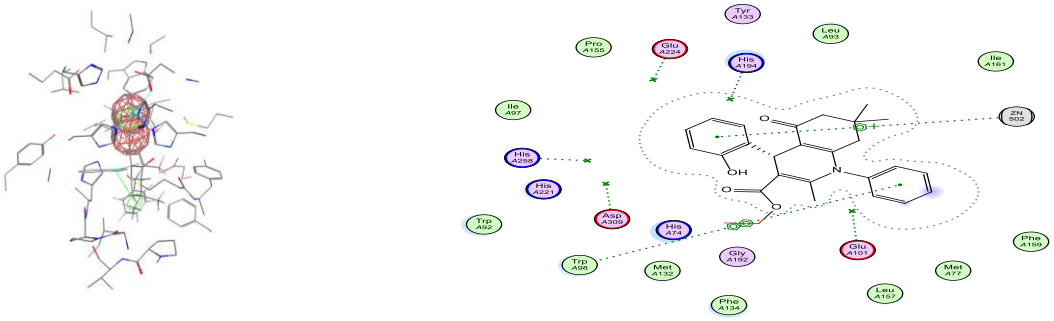

Figure26. Showed 3D and 2D, interaction of Q5. Ethyl 4-(2-hydroxyphenyl)-2,7,7-trimethyl-5-oxo-1-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate inside the active site of 4gdb protein.

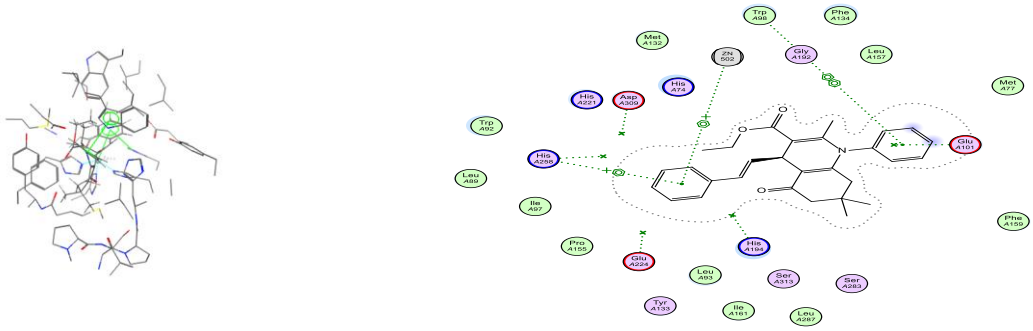

Figure27. Showed 3D and 2D, interaction of Q6. Ethyl (E)-2,7,7-trimethyl-5-oxo-1-phenyl-4-styryl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate inside the active site of 4gdb protein.

العدد أربعون
تاريخ الإصدار: 2 – شباط – 2022 م
www.ajsp.net
ISSN: 2663-5798

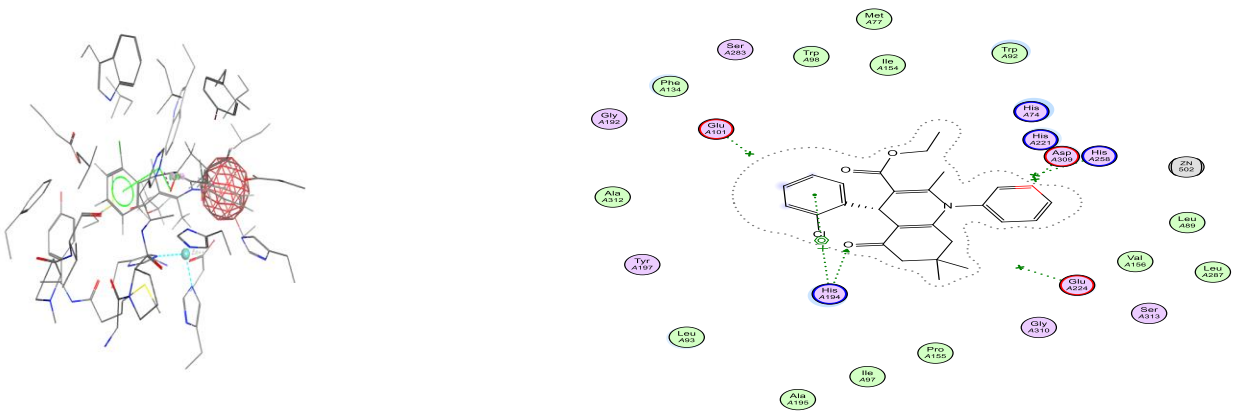

Figure28. Showed 3D and 2D, interaction of Q7. Ethyl 4-(2-chlorophenyl)-2,7,7-trimethyl-5-oxo-1-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate inside the active site of 4gdb protein.

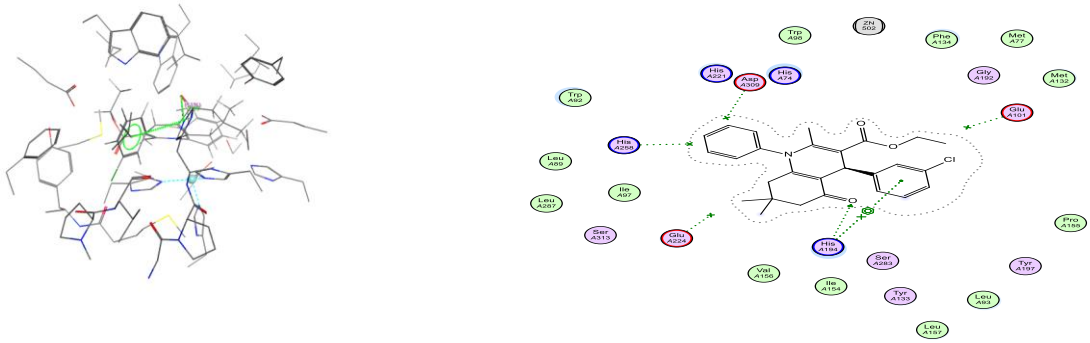

Figure 29. Showed 3D and 2D, interaction of Q8. Ethyl 4-(3-chlorophenyl)-2,7,7-trimethyl-5-oxo-1-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate inside the active site of 4gdb protein.

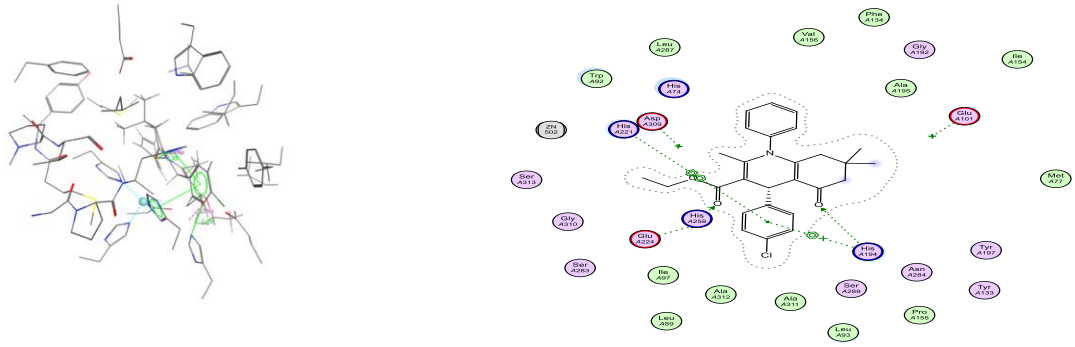

Figure 30. Showed 3D and 2D, interaction of Q9. Ethyl 4-(4-chlorophenyl)-2,7,7-trimethyl-5-oxo-1-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate inside the active site of 4gdb protein.

العدد أربعون
تاريخ الإصدار: 2 – شباط – 2022 م
www.ajsp.net
ISSN: 2663-5798

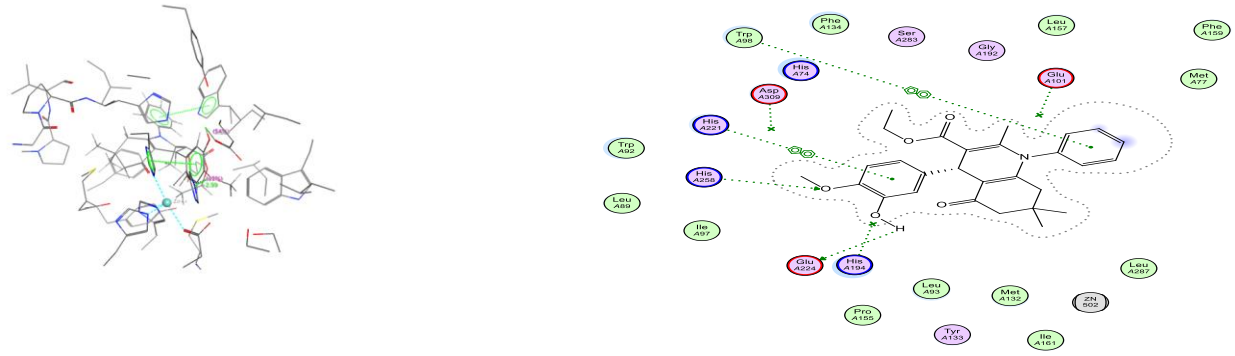

Figure31. Showed 3D and 2D, interaction of Q10. Ethyl 4-(3-hydroxy-4-methoxyphenyl)-2,7,7-trimethyl-5-oxo-1-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate inside the active site of 4gdb protein.

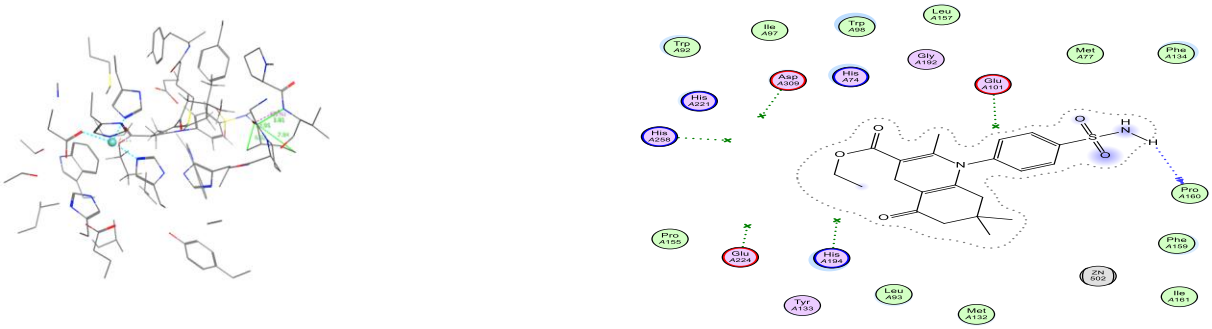

Figure32. Showed 3D and 2D, interaction of Q11. Ethyl 2,7,7-trimethyl-5-oxo-1-(4-sulfamoylphenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate inside the active site of 4gdb protein.

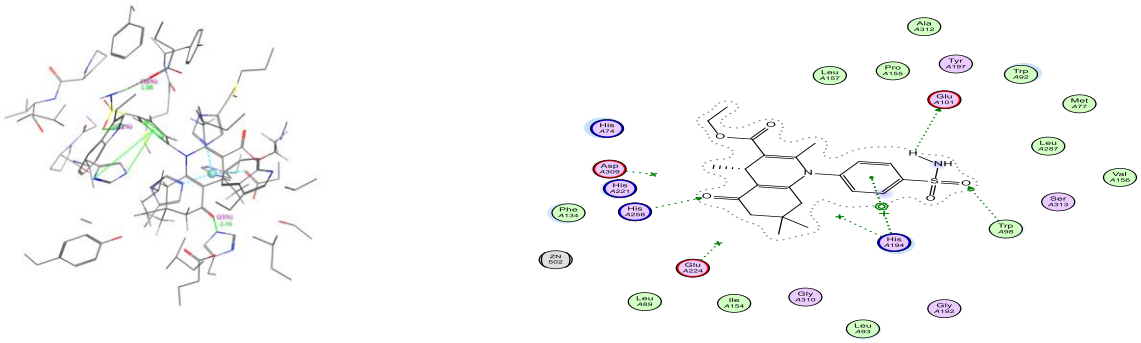

Figure33. Showed 3D and 2D, interaction of Q12. Ethyl 2,4,7,7-tetramethyl-5-oxo-1-(4-sulfamoylphenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate inside the active site of 4gdb protein.

العدد أربعون
تاريخ الإصدار: 2 – شباط – 2022 م
www.ajsp.net
ISSN: 2663-5798

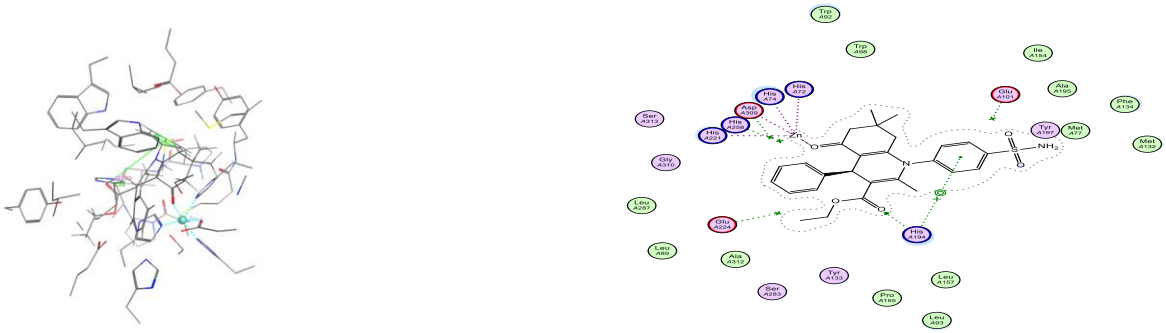

Figure34. Showed 3D and 2D, interaction of Q13. Ethyl 2,7,7-trimethyl-5-oxo-4-phenyl-1-(4-sulfamoylphenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate inside the active site of 4gdb protein.

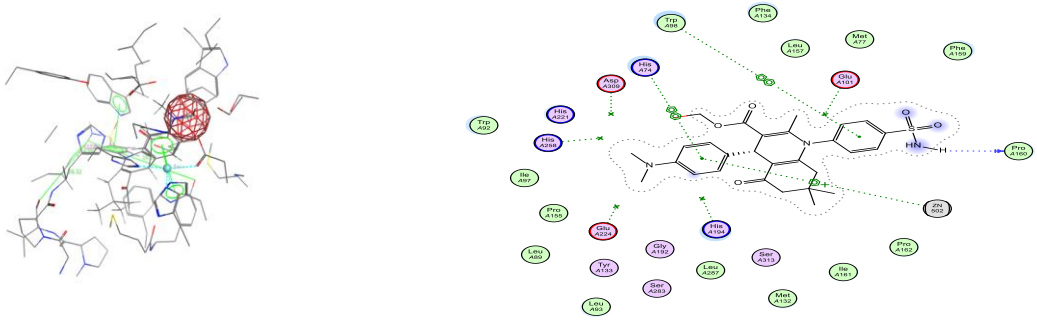

Figure35. Showed 3D and 2D, interaction of Q14. Ethyl 4-(4-(dimethylamino)phenyl)-2,7,7-trimethyl-5-oxo-1-(4-sulfamoylphenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate inside the active site of 4gdb protein.

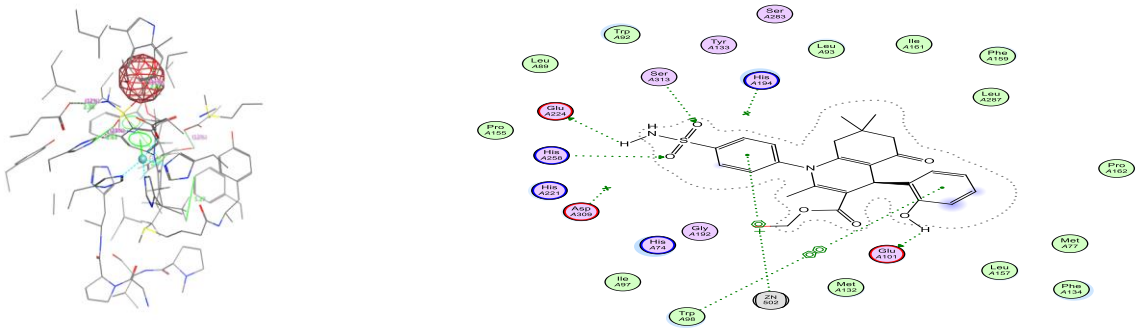

Figure36. Showed 3D and 2D, interaction of Q15. Ethyl 4-(2-hydroxyphenyl)-2,7,7-trimethyl-5-oxo-1-(4-sulfamoylphenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate inside the active site of 4gdb protein.

العدد أربعون
تاريخ الإصدار: 2 – شباط – 2022 م
www.ajsp.net
ISSN: 2663-5798

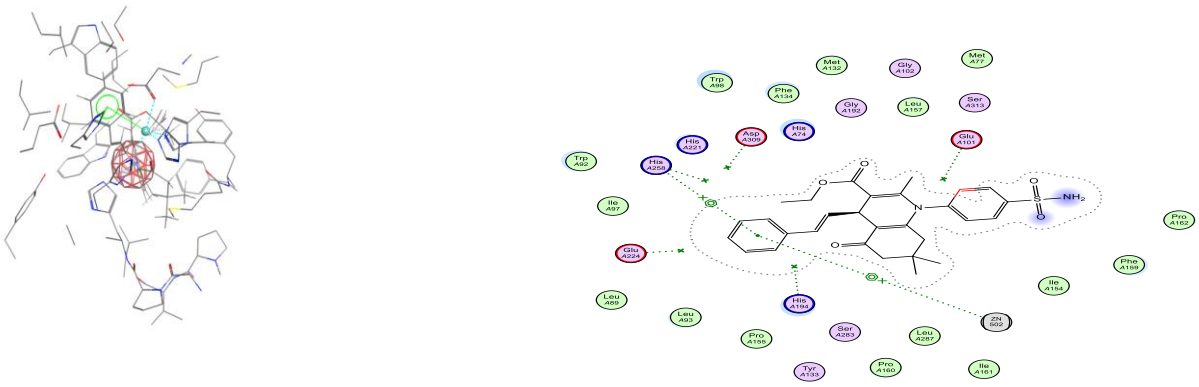

Figure37. Showed 3D and 2D, interaction of Q16. Ethyl (E)-2,7,7-trimethyl-5-oxo-4-styryl-1-(4-sulfamoylphenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate inside the active site of 4gdb protein.

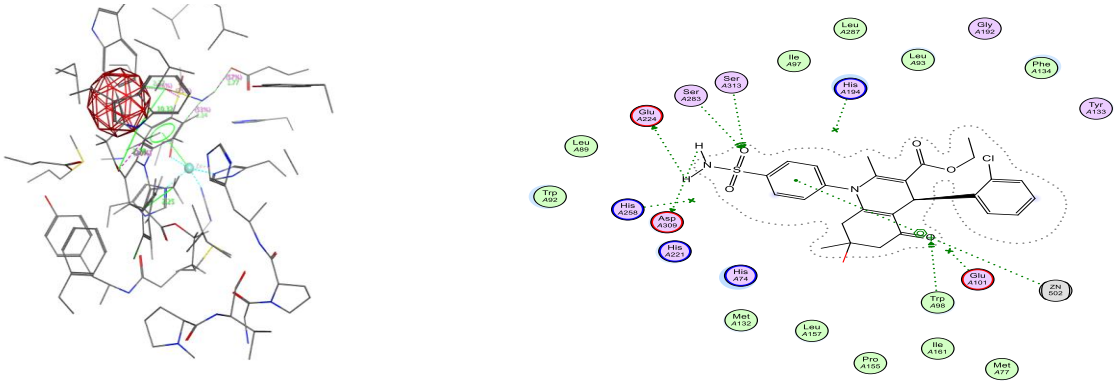

Figure38. Showed 3D and 2D, interaction of Q17. Ethyl 4-(2-chlorophenyl)-2,7,7-trimethyl-5-oxo-1-(4-sulfamoylphenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate inside the active site of 4gdb protein.

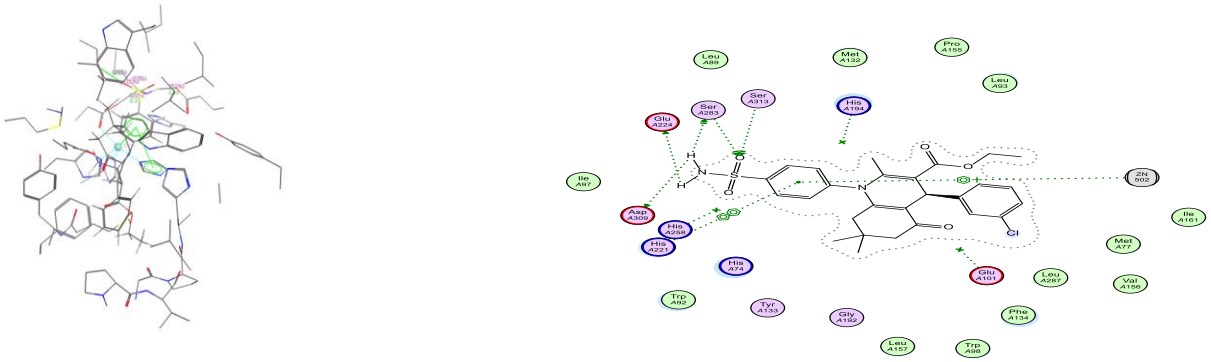

Figure39. Showed 3D and 2D, interaction of Q18. Ethyl 4-(3-chlorophenyl)-2,7,7-trimethyl-5-oxo-1-(4-sulfamoylphenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate inside the active site of 4gdb protein.

العدد أربعون
تاريخ الإصدار: 2 – شباط – 2022 م
www.ajsp.net
ISSN: 2663-5798

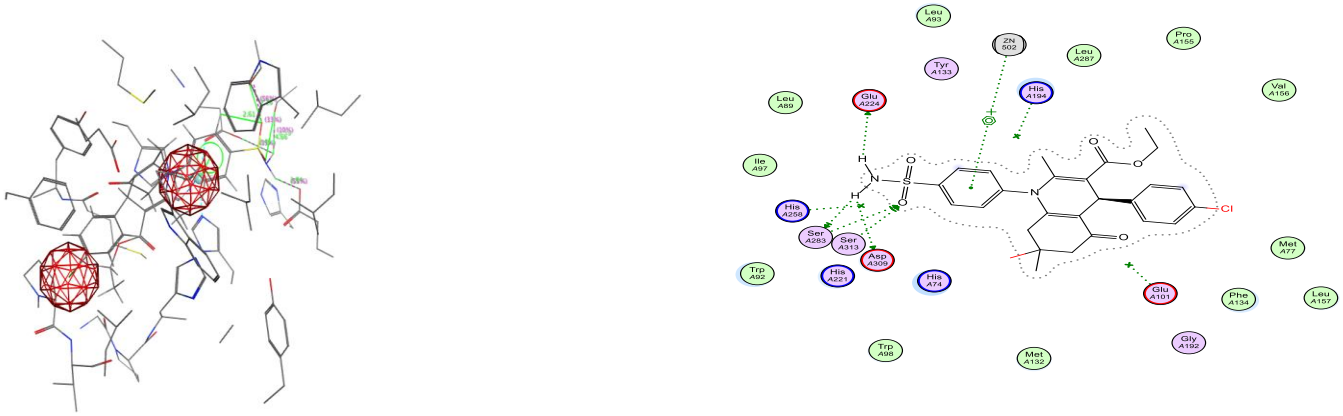

Figure40. Showed 3D and 2D, interaction of Q19. Ethyl 4-(4-chlorophenyl)-2,7,7-trimethyl-5-oxo-1-(4-sulfamoylphenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate inside the active site of 4gdb protein.

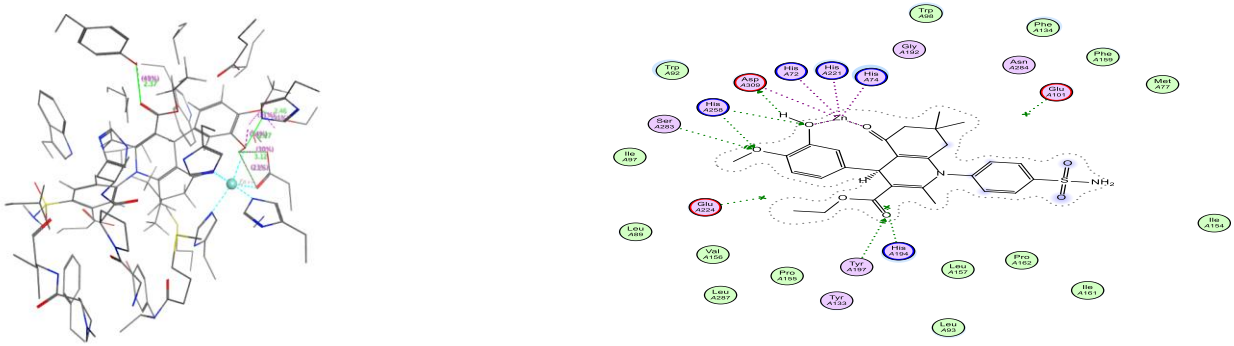

Figure41. Showed 3D and 2D, interaction of Q20. Ethyl 4-(3-hydroxy-4-methoxyphenyl)-2,7,7-trimethyl-5-oxo-1-(4-sulfamoylphenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate inside the active site of 4gdb protein.

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